

Substitution Form 249A/PTO

INFORMATION DISCLOSURE
STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 Of 4

Application Number 09/873,899

Filing Date June 4, 2001

First Named Inventor Ekwuribe

Group Art Unit 1654

Examiner Name Russel, Jeffrey E.

Attorney Docket Number 9233.54

U.S. PATENT DOCUMENTS

Class / Subclass

Pages, Columns, Lines, Where
Relevant Passages or Relevant
Figures Appear

Examiner Initials*	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number	Kind Code			
JR	1.	2002/0160938	A1	Brandenburg et al.	10/31/2002	514/13
JR	2.	2003/0144468	A1	Ekwuribe et al.	07/31/2003	528/425
JR	3.	2003/0087808	A1	Soltero et al.	05/08/2003	514/3
JR	4.	2003/0083232	A1	Soltero et al.	05/01/2003	514/3
JR	5.	2003/0069170	A1	Soltero et al.	04/10/2003	514/2
JR	6.	2003/0060606	A1	Ekwuribe et al.	03/27/2003	530/399
JR	7.	2003/0050228	A1	Ekwuribe et al.	03/13/2003	514/3
JR	8.	2003/0027995	A1	Ekwuribe et al.	02/06/2003	530/399
JR	9.	2003/0004304	A1	Ekwuribe et al.	01/02/2003	528/425
JR	10.	4,602,043		Geho	07/22/1986	514/646
JR	11.	4,662,872		Cané	05/05/1987	604/151
JR	12.	4,704,394		Geho	11/03/1987	514/288
JR	13.	4,761,287		Geho	08/02/1988	424/450
JR	14.	4,822,337		Newhouse et al.	04/18/1989	604/50
JR	15.	4,863,896		Geho et al.	09/05/1989	514/4
JR	16.	4,963,526		Ecanow	10/16/1990	514/3
JR	17.	5,320,094	A	Laube et al.	06/14/1994	128/203.12
JR	18.	5,321,009	A	Baeder et al.	06/14/1994	514/4
JR	19.	5,364,838	A	Rubsamen	11/15/1994	514/3
JR	20.	5,420,108	A	Shohet	05/30/1995	514/3
JR	21.	5,468,727	A	Phillips et al.	11/21/1995	514/12
JR	22.	5,597,797	A	Clark et al.	01/28/1997	514/12
JR	23.	5,681,567	A	Martinez et al.	10/28/1997	424/178.1
JR	24.	5,704,910	A	Humes	01/06/1998	604/52
JR	25.	5,714,519	A	Cincotta et al.	02/03/1998	514/616
JR	26.	5,763,396	A	Weiner et al.	06/09/1998	514/3
JR	27.	5,843,866	A	Weiner et al. Parker et al.	12/01/1998	504/116
JR	28.	5,866,584	A	Cincotta et al.	02/02/1999	514/288
JR	29.	5,997,848	A	Patton et al.	12/07/1999	424/46
JR	30.	6,042,822	A	Gilbert et al.	03/28/2000	424/85.7
JR	31.	6,057,292	A	Cunningham et al.	05/02/2000	514/12
JR	32.	6,147,108	A	Hauptman	11/14/2000	514/449
JR	33.	6,342,225	B1	Jones et al.	01/29/2002	424/193.1
JR	34.	6,506,730	B1	Lee et al.	01/14/2003	514/12

FOREIGN PATENT DOCUMENTS

Class / Subclass

Pages, Columns, Lines, Where
Relevant
Passages/Figures Appear

Examiner Initials*	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages/Figures Appear	T
		Office	Number	Kind Code (if known)				
JR	35.	EP	EP 0 511 903	B1	Wantier et al.	10/14/1998		Claims
JR	36.	WO	99/65941	A1	Jones et al.	12/23/1999		

OTHER NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T
JR	37.	Agarwal et al. "Polymethacrylate-based Microparticulates of Insulin for Oral Delivery: Preparation and In Vitro Dissolution Stability in the Presence of Enzyme Inhibitors" <i>International Journal of Pharmaceutics</i> 225:31-39 (2001)	

Examiner Signature

Jeffrey E. Russel

Date Considered

December 24, 2003

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 2 Of 4

Application Number 09/873,899

Filing Date June 4, 2001

First Named Inventor Ekwuribe

Group Art Unit 1654

Examiner Name Russel, Jeffrey E.

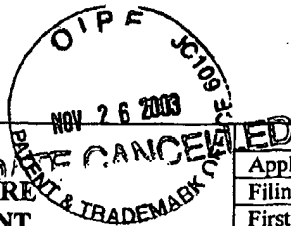
Attorney Docket Number 9233.54

OTHER NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T
	38.	Allaudeen et al. "Orally Active Insulin: A Single Insulin Conjugate Selected for Future Studies" 60 th Annual Meeting of the American Diabetes Assoc., Atlanta, GA June 2000 (Abstract)	
	39.	Anderson et al. "HIM2, a Novel Modified Insulin, has Improved Systemic Pharmacokinetics in Normal Dogs, Compared to Unmodified Insulin" American Diabetes Association 62 nd Annual Meeting June 2002 (Abstract)	
	40.	Block, Lawrence H. "Pharmaceutical Emulsions and Microemulsions" <i>Pharmaceutical Dosage Forms: Disperse Systems</i> , Vol. 2, Ed. Lieberman et al. (1996)	
	41.	Bone et al. "Successful Treatment of an Insulin Dependent Rat Model of Human Type I Diabetes with Orally Active Insulin" Program and Abstracts, 4 th International Workshop on Lessons from Animal Diabetes, Omiya, Japan November 1994 (Abstract)	
	42.	Bone et al. "Successful Treatment of Type 1 Diabetes with Orally-Active Insulin: Studies in The Insulin Dependent BB/S Rat" Program and Abstracts, 55 th Annual Meeting of the American Diabetes Association, Atlanta Georgia, June 1995 (Abstract)	
	43.	Brange and Volund "Insulin Analogs with Improved Pharmacokinetic Profiles" <i>Advanced Drug Delivery Reviews</i> 35:307-335 (1999)	
	44.	Cleland et al. "Emerging Protein Delivery Methods" <i>Current Opinion in Biotechnology</i> 12:212-219 (2001)	
	45.	Clement et al. "Effects of Multiple Doses of Orally Administered Hexyl Insulin M2 (HIM2) on Postprandial Blood Glucose (PPG) Concentrations in Type 1 Diabetic (T1) Patients" American Diabetes Association 62 nd Annual Meeting, June 2002 (Poster)	
	46.	Clement et al. "Oral Insulin Product Hexyl-Insulin Monoconjugate 2 (HIM2) in Type 1 Diabetes Mellitus: The Glucose Stabilization Effects of HIM2" <i>Diabetes Technology & Therapeutics</i> 4(4):459-466 (2002)	
	47.	Clement, Stephen "A Dose-Escalation Study of the Effects of Two Sequential Doses of Oral Modified Insulin on Blood Glucose Concentrations in Patients with Type 1 Diabetes Mellitus" American Diabetes Association Annual Meeting (June 25, 2001) (Abstract)	
	48.	Damge et al. "Poly(alkyl cyanoacrylate) Nanospheres for Oral Administration of Insulin" <i>Journal of Pharmaceutical Sciences</i> 86(12):1403-1409 (Dec. 1997)	
	49.	Dandona et al. "Effect of an Oral Modified Insulin on Blood Glucose Levels in Fasting and Fed Type 1 Diabetic Patients Receiving a "Basal" Regimen of Injected Insulin" American Diabetes Association Annual Meeting (June 25, 2001) (Abstract)	
	50.	Ekwuribe et al. "Calcitonin Drug-Oligomer Conjugates, and Uses Thereof" U.S. Serial No. 10/166,355, filed 11/08/2002, including Preliminary Amendment dated 02/26/2003 and Supplemental Preliminary Amendment dated 03/31/2003	
	51.	Ekwuribe et al. "Mixtures of Drug-Oligomer Conjugates Comprising Polyalkylene Glycol, Uses Thereof, and Methods of Making Same" U.S. Serial No. 09/873,797, filed 06/04/2001	
	52.	Ekwuribe et al. "Oral Insulin Delivery: Hydrolyzable Amphiphilic Oligomer Conjugates Prolong Glucose Reduction" <i>Proceed. Int'l. Symp. Control. Rel. Bioact. Mater.</i> 26:147-148 (1999)	
	53.	Ekwuribe, Nnochiri "Conjugation-Stabilized Polypeptide Compositions, Therapeutic Delivery and Diagnostic Formulations Comprising Same, and Method of Making and Using the Same" <i>Biotechnology Advances</i> 14(4):575-576 (1996) (Abstract)	
	54.	Hinds et al. "Synthesis and Characterization of Poly(ethylene glycol)-Insulin Conjugates" <i>Bioconjugate Chem.</i> 11:195-201 (2000)	

Examiner Signature Jeffrey E. Russel Date Considered December 24, 2003

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.



Substitute form 1449A/PTO

INFORMATION DISCLOSURE
STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 3 Of 4

Complete if Known

Application Number	09/873,899
Filing Date	June 4, 2001
First Named Inventor	Ekwuribe
Group Art Unit	1654
Examiner Name	Russel, Jeffrey E.
Attorney Docket Number	9233.54

OTHER NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T
	55.	Kipnes et al. "Control of Postprandial Plasma Glucose by an Oral Insulin Product (HIM2) in Patients with Type 2 Diabetes" <i>Emerging Treatments and Technologies</i> 26:2 (2003)	
	56.	Kipnes et al. "The Effects of an Oral Modified Insulin on Postprandial Blood Glucose Levels in Patients with Type 2 Diabetes" American Diabetes Association Annual Meeting (June 24, 2001) (Abstract)	
	57.	Kipnes et al. "The Effects of an Oral Modified Insulin on Postprandial Blood Glucose Levels in Patients with Type 2 Diabetes Mellitus" American Diabetes Association Annual Meeting (June 24, 2001) (Poster)	
	58.	Kube, D.M. "Multitalented Proteins Play a Key Role in Therapeutics" <i>Genomics and Proteomics</i> (Sept. 2002)	
	59.	Marschutz et al. "Oral Peptide Drug Delivery: Polymer-Inhibitor Conjugates Protecting Insulin from Enzymatic Degradation In Vitro" <i>Biomaterials</i> 21:1499-1507 (2000)	
	60.	Musabayane et al. "Orally Administered, Insulin-Loaded Amidated Pectin Hydrogel Beads Sustain Plasma Concentrations of Insulin in Streptozotocin-Diabetic Rats" <i>Journal of Endocrinology</i> 164:1-6 (2000)	
	61.	Pang, David C. "Bridging Gaps in Drug Discovery and Development" <i>Pharmaceutical Technology</i> 82-94 (Nov.1998)	
	62.	Pauletti et al. "Improvement of Oral Peptide Bioavailability: Peptidomimetics and Prodrug Strategies" <i>Advanced Drug Delivery Reviews</i> 27:235-256 (1997)	
	63.	Puskas et al. "Investigation of Chymotrypsin Digestion Profile of Orally Active Insulin Conjugate HIM2" <i>AAPS Pharm. Sci.</i> 3(3) 2001 (Abstract)	
	64.	Radhakrishnan et al. "Chemical Modification of Insulin with Amphiphilic Polymers Improves Intestinal Delivery" <i>Proceed. Intl. Symp. Control. Rel. Bioact. Mater.</i> 25:124-125 (1998) (Abstract)	
	65.	Radhakrishnan et al. "Oral Delivery of Insulin: Single Selective Modification at B29-LYS With Amphiphilic Oligomer" Program and Abstracts, 1999 National Meeting of the Ameri. Assoc. Pharm. Scient., New Orleans, LA (1999) (Abstract)	
	66.	Radhakrishnan et al. "Structure-Activity Relationship of Insulin Modified with Amphiphilic Polymers" Program and Abstracts, 1998 National Meeting of the Amer. Assoc. Pharm. Scient., San Francisco, CA <i>Pharm. Sci.</i> 1(1):S-59 (1998) (Abstract)	
	67.	Radhakrishnan et al., "Insulin Polypeptide-Oligomer Conjugates, Proinsulin Polypeptide-Oligomer Conjugates and Methods of Synthesizing Same" U.S. Serial No. 10/389,499, filed 03/17/2003	
	68.	Richards et al. "Self-Association Properties of Monomeric Insulin Analogs Under Formulation Conditions" <i>Pharmaceutical Research</i> 15(9):1434-1441 (1998)	
	69.	Shah and Shen "Transcellular Delivery of an Insulin-Transferrin Conjugate in Enterocyte-like Caco-2 Cells" <i>Journal of Pharmaceutical Sciences</i> 85(12):1306-1311 (1996)	
	70.	Sluzky et al. "Kinetics of Insulin Aggregation in Aqueous Solutions Upon Agitation in the Presence of Hydrophobic Surfaces" <i>Proc. Natl. Acad. Sci.</i> 88:9377-9381 (Nov. 1991)	
	71.	Soltero et al. "Insulin Polypeptide-Oligomer Conjugates, Proinsulin Polypeptide-Oligomer Conjugates and Methods of Synthesizing Same" U.S. Serial No. 10/382,022, filed 03/05/2003	
	72.	Soltero et al. "Pharmaceutical Compositions of Drug-Oligomer Conjugates and Methods of Treating Diseases Therewith" U.S. Serial No. 10/382,069, filed 03/05/2003	
	73.	Soltero et al. "Pharmaceutical Compositions of Insulin Drug-Oligomer Conjugates and Methods of Treating Diseases Therewith" U.S. Serial No. 10/382,155, filed 03/05/2003	
	74.	Song et al. "Direct Measurement of Pulsatile Insulin Secretion from the Portal Vein in Human Subjects" <i>Journal of Clinical Endocrinology & Metabolism</i> 85(12):4491-4499 (2000)	

Substitute form 1449A/PTO

Complete if Known

Examiner Signature

Jeffrey E. Russel

Date Considered

December 23, 2003

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

DATE CANCELLED

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(use as many sheets as necessary)

Sheet	4	Of	4	Application Number	09/873,899
				Filing Date	June 4, 2001
				Inventor	Ekwuribe
				Group Art Unit	1654
				Examiner Name	Russel, Jeffrey E.
				Attorney Docket Number	9233.54

OTHER RUN PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T
	75.	Still and McAllister "Effects of Orally Active Modified Insulin in Type I Diabetic Patients" <i>Clinical Pharmacol. Therap.</i> 69(2): P95 (Feb. 2001) (Abstract)	
	76.	Still and McAllister "Effects of Orally Active Modified Insulin in Type I Diabetic Patients" Slide Presentation 2001 Annual Meeting of the American Society for Clinical Pharmacology & Therapeutics, Orlando, FL, March 9, 2001	
	77.	Still and McAllister "Effects of Orally Active Modified Insulin in Type I Diabetic Patients" 2001 Annual Meeting of the American Society for Clinical Pharmacology & Therapeutics, Orlando, FL, March 9, 2001 (Handout)	
	78.	Still et al. "Magnitude and Variability of Pharmacokinetic and Glucodynamic Responses to Modified Human Insulin Administered Orally to Healthy Volunteers" <i>Diabetes Research and Clinical Practice</i> 56:S77 (2002)	
	79.	Still et al. "Methods of Reducing Hypoglycemic Episodes in the Treatment of Diabetes Mellitus" U.S. Serial No. 10/461,199, filed 06/13/2003	
	80.	Still, J. Gordon "Development of Oral Insulin: Progress and Current Status" <i>Diabetes/Metabolism Research and Reviews</i> , 18(1):S29-S37 (2002)	
	81.	Still, J. Gordon "Oral Insulin Development" Slide Presentation, VI International St.Barts Symposium Diabetes 2000: Therapy and Technology, London, England, May 12, 2000	
	82.	Stocklin et al. "A Stable Isotope Dilution Assay for the In Vivo Determination of Insulin Levels in Humans by Mass Spectrometry" <i>Diabetes</i> 46(1):1-7 (Jan. 1997)	
	83.	Tyle, Praveen "Iontophoretic Devices for Drug Delivery" <i>Pharmaceutical Research</i> 3(6):318-326 (1986)	
	84.	Uchio et al. "Site-Specific Insulin Conjugates with Enhanced Stability and Extended Action Profile" <i>Advanced Drug Delivery Reviews</i> 35:289-306 (1999)	
	85.	Vreeland et al. "Molar Mass Profiling of Synthetic Polymers by Free-Solution Capillary Electrophoresis of DNA-Polymer Conjugates" <i>Anal. Chem.</i> 73(8):1795-1803 (2001)	
	86.	Ziv and Bendayan "Intestinal Absorption of Peptides Through the Enterocytes" <i>Microscopy Research and Technique</i> 49:346-352 (2000)	

Examiner Signature	Jeffrey E. Russel	Date Considered	December 24, 2003
--------------------	-------------------	-----------------	-------------------

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.